REMARKS

Please enter this Amendment and Response.

Applicants have cancelled claims 52-53 without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of these claims in one or more continuation applications.

Applicants have amended claims 25, 44, 49, 54, 58, 60, and 64. The amendments are supported throughout the specification, including at page 11, lines 20 to 27; page 20, lines 5-7; page 30, lines 26-27, and original claim 11.

Applicants have added new claims 66 and 67. Applicants submit the new claims are supported throughout the specification including at page 20, lines 5-7; page 30, lines 26-27, and original claim 11.

OBJECTION TO THE SPECIFICATION

The Examiner objected to the specification for referring cys-pro-pro-cys by "CPC" instead of "CPPC". While not acquiescing to the Examiner's statements, Applicants have amended the specification to refer to "CPPC" at page 30, line 22. Applicants request withdrawal of this rejection.

35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner rejected claims 25, 39, 43-44 and 49-65 under 35 U.S.C. § 112, first paragraph, written description. The Examiner contends the specification lacks support for the language "an amino acid sequence of up to 10 amino acids, wherein the amino acid sequence of about up to 10 amino acids comprises a C terminal amino acid sequence of Cys-Ala-Ala". The Examiner contends that a species or a genus does not necessarily provide written description for a subgenus. Applicants respectfully traverse.

Applicants note that there is a strong presumption that an adequate written description of the claimed invention exists. (See MPEP 2163.II.A.) To adequately describe the claims, the specification need not describe ipsis verbis what is recited in the claims; rather, the claim limitations may be supported in the specification through implicit or inherent disclosure rather than express disclosure. (MPEP 2163 I.B.) Even if

the specification does not explicitly recite a claim limitation, sufficient written description exists for the limitation if one of skill in the art can "immediately discern the limitation" from reading the original specification. *Waldemar Link, GmbH & Co. v. Osteonics Corp.*, 31 USPQ2d 1855 (Fed Cir. 1994). "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met." (MPEP 2163 II.A.3(a).) If the specification contains a description of the invention, although not *ipsis verbis*, then the Examiner must provide reasons why one of skill in the art would not consider the description sufficient. In Re Alton, 76 F3d 1168 (Fed. Cir. 1996). In light of the foregoing standards, the present claims are clearly described by the specification.

Applicants' claim 25 is now directed to a composition comprising a monospecific $F(ab')_2$, wherein the $F(ab')_2$ comprises a first and second Fab', wherein each Fab' has a single hinge region cysteine residue and comprises a C terminal amino acid sequence of Cys-Ala-Ala, and wherein the monospecific $F(ab)_2$ lacks glycosylation. Applicant's claim 44 is directed to a composition comprising a monospecific $F(ab')_2$ produced by the process of expressing a nucleic acid sequence encoding an inducible promoter operably linked to nucleic acid encoding a Fab' in a microbial host cell under conditions suitable for secretion of the Fab' to the periplasmic space; wherein the Fab' has a single hinge region cysteine residue and comprises a C terminal amino acid sequence of Cys-Ala-Ala; and recovering the Fab' from the host cell and coupling the free thiol of each Fab' to form the monospecific $F(ab')_2$. Applicant's claim 60 is directed to a composition comprising a monospecific $F(ab')_2$ produced by the process of expressing a nucleic acid under the control of an inducible promoter, wherein the nucleic acid encodes a Fab' in a microbial host cell under conditions suitable for secretion of the Fab' to the periplasmic space, wherein the Fab' comprises a heavy chain CH1 domain fused to one or more cysteines or a cysteine-containing polypeptide of about 1-10 residues in place of an immunoglobulin hinge region, and wherein the cysteine containing polypeptide has a single cysteine residue; and recovering the Fab' from the host cell and coupling the free

thiol of each Fab' to form the monospecific $F(ab')_2$, and wherein the monospecific $F(ab')_2$ lacks glycosylation.

Applicants' claim 49 is directed to a composition comprising a Fab' coupled to a heterologous molecule produced by the process of expressing a nucleic acid sequence encoding an inducible promoter operably linked to a nucleic acid encoding a Fab' in a microbial host cell under conditions suitable for secretion of the Fab' to the periplasmic space; wherein the Fab' comprises has a single hinge region cysteine residue and a C terminal amino acid sequence of Cys-Ala-Ala; and recovering the Fab' from the host cell and coupling the free thiol of the Fab' with the heterologous molecule and wherein the Fab' lacks glycosylation. Applicant's claim 54 is directed to a composition comprising a Fab' fragment coupled to a heterologous molecule produced by the process of expressing a nucleic acid under the control of an inducible promoter, wherein the nucleic acid encodes a light chain variable domain, a heavy chain variable domain and a CH1 domain fused to one or more cysteines or a cysteine-containing polypeptide of about 1-10 amino acid residues in place of an immunoglobulin hinge region in a microbial host cell under conditions suitable for secretion of the antibody fragment to the periplasmic space, and wherein the cysteine containing polypeptide has a single cysteine residue; and recovering the Fab' from the host cell and coupling the free thiol of the Fab' with the heterologous molecule.

Applicants submit that one of ordinary skill in the art would understand that Applicants were in possession of the invention as claimed. Applicants submit the specification provides written description for a genus, subgenus and a species. Applicants further submit that the examples are not necessary to support the adequacy of written description, written description can be met where actual reduction to practice is absent; and there is no per se rule that an adequate written description that involves a biological macromolecule must contain a recitation of known structure. Falko-Gunter Falkner vs. Inglis,448 F.3d 1357 (Fed. Cir. 2006). In addition, the description should be evaluated with the scientific and technologic knowledge at the time of filing. Id at 1363.

As an initial matter, Applicants note that the language in claims 25, 44 and 49 is language which appears in the specification at least on page 30, lines 26-27. Applicants

also note that language of claims 54 and 60 is language which appears in the specification at least on page 11, lines 20-27.

Applicants submit, that in contrast to the Examiner's position, the specification does describe several subgenuses including a subgenus of a Fab' comprising a cysteine containing polypeptide of up to 10 amino acids and comprising a C terminal sequence Cys-Ala-Ala. As described in the specification and exemplified in the examples, a single cysteine containing polypeptide of up to 10 amino acids can have other amino acids and a single cysteine residue that is present in the C terminal amino acid sequence. As described in the specification, the Fv light or heavy chains are fused to a polypeptide sequence which contains one or more cysteine residues. (See e.g. page 6, lines 15-34, and page 11, lines 20-22.) Several subgenuses are described including a Fv-CH1 domain fused to a hinge region sequence variant that contains only a single cysteine residue or any other sequence containing a single free thiol cysteinyl residue in place of the immunoglobulin hinge region. (See e.g., page 6, lines 26-31 and lines 26-28.)

In addition, at page 11, the specification describes that a Fab' has at least one additional amino acid at the carboxy terminus of the heavy chain including one or more cysteine residues. (See, e.g., page 11, lines 20-22) The specification indicates that the Fab' may include a hinge region or, alternatively, the hinge may be entirely omitted in favor of one or more cysteine residues or preferably a short (about 1 to 10 residues) cysteine containing polypeptide. (See e.g., page 11, lines 24-27.) In that same paragraph, the specification describes that in certain embodiments, the C terminus of the CH1 of Fab' is fused to the sequence Cys-X-X, wherein X is Ala or may be any other residue such as Arg, Asp, or Pro and one of both X amino acids may be deleted. (See e.g., page 11, lines 32-35). This Cys-X-X is a subgenus of at least the short (about 1 to 10 residues) cysteine containing polypeptide. A species of at least the short (about 1 to 10 residues) cysteine containing polypeptide includes the sequence of Cys-Ala-Ala. The language at page 30, line 26-27 provides that the Fab' variant has a C terminal amino acid sequence of Cys-Ala-Ala. The original claims describe a Fab' polypeptide having at least one cysteine in a hinge region present as a free thiol (original claim 2) including a Fab' comprising the C terminal amino acid sequence Cys-Ala-Ala (original claim 11 which is

dependent on claim 2). These claims provide explicit support for the subgenus as claimed. Features of a Fab' that are described throughout the specification are a Fab' having at least one cysteine present as a free thiol and that the cysteine having the free thiol is present at the C terminus of the heavy chain, whether part of a variant hinge or part of a short (about 1 to 10 residues) cysteine containing polypeptide in place of the hinge region. Applicant's submit that one of skill in the art reading the specification would conclude that a Fab' as described in the specification can have a short (about 1 to 10 residues) cysteine containing polypeptide in place of a hinge region and that the Fab' can comprise a C terminal amino acid sequence Cys- Ala-Ala.

While not acquiescing to the Examiner's position, Applicants' claim 25 now refers to a $F(ab')_2$, wherein each Fab' has a single hinge region cysteine residue and has a C terminal amino acid sequence of Cys-Ala-Ala. Claim 44 is directed to a $F(ab')_2$ prepared by a method, wherein a nucleic acid encodes an inducible promoter operably linked to a nucleic acid encoding a Fab' under conditions suitable for secretion to the periplasmic space, wherein the Fab' has a single hinge region cysteine residue and has a C terminal amino acid sequence of Cys-Ala-Ala. Claim 60 is directed to a composition comprising a monospecific $F(ab')_2$ produced by the process of expressing a nucleic acid under the control of an inducible promoter wherein the nucleic acid encodes a Fab' in a microbial host cell under conditions suitable for secretion of the Fab' to the periplasmic space; wherein the Fab' comprises a heavy chain CH1 domain fused to one or more cysteines or a cysteine-containing polypeptide of about 1-10 residues in place of an immunoglobulin hinge region. Applicants submit that the specification describes methods of making $F(ab')_2$ throughout the specification, for example, at page 14, lines 5-25 and page 23, lines 20-30. Applicants demonstrate making a Fab' variant with these characteristics and describe that other Fab' variants can be made using cassette mutagenesis. (See, e.g., the specification at page 30, lines 1-30.) Applicants submit that in the least they have written description for that which they have exemplified and described including methods for producing other Fab' variants using, for example, cassette mutagenesis.

Finally, Applicants' claim 49 is directed to a composition comprising a Fab' coupled to a heterologous molecule produced by the process of expressing a nucleic acid sequence encoding an inducible promoter operably linked to a nucleic acid encoding a Fab' in a microbial host cell under conditions suitable for secretion of the Fab' to the periplasmic space; wherein the Fab' has a single hinge region cysteine residue and has a C terminal amino acid sequence of Cys-Ala-Ala. Applicant's claim 54 is directed to a composition comprising a Fab' fragment coupled to a heterologous molecule produced by the process of expressing a nucleic acid under the control of an inducible promoter wherein the nucleic acid encodes a light chain variable domain, a heavy chain variable domain and a CH1 domain fused to one or more cysteines or a cysteine-containing polypeptide of about 1-10 amino acid residues in place of an immunoglobulin hinge region. Applicants submit that a Fab' having these characteristics is described in the specification, including at page 6, lines 30-31 and page 11, lines 24-27. A species of a short cysteine containing polypeptide is a Fab' having a single hinge region cysteine and having a C terminal amino acid sequence Cys-Ala-Ala as described in the working example . (See, e.g., the specification at page 30, lines 26-27.) Again, the specification describes the genus, subgenus, and exemplifies at least one species and Applicants submit that, therefore, one of skill in the art would understand that Applicants were in possession of the claimed subject matter.

Based on the foregoing, Applicants request withdrawal of 35 U.S.C. § 112 rejection.

SUMMARY

Applicant submits the claims are in condition for allowance and notification to that effect is earnestly solicited. Applicant requests that the Examiner contact Applicant's representative if prosecution may be assisted thereby.

Respectfully submitted,

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